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THE RELATIONSHIP OF BRACHYDACTYLY AND JOINT RANGE OF MOTION IN A KASHIN-BECK DISEASE REGION OF CHINA

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Purpose: Kashin-Beck Disease (KBD) is an osteoarthropathy of uncertain etiology that is endemic to the central and northwest regions of China. Affected individuals have varying degrees of joint deformity and limited joint mobility. Until now, the gold standard for the diagnosis of KBD has been based on radiographic and clinical examination features. Nevertheless, it is still difficult for grass-roots health care workers and medical researchers to diagnose KBD. We studied the relationship of one of the signs of KBD—brachydactyly, and the range of motion (ROM) at 8 joint sites. Our long-term goal is to improve the sensitivity and specificity of the screening tools for KBD.
Methods: 125 subjects from the Shangqiu village located in Shaanxi province were involved in this study. All study procedures were approved by the Xi'an Jiongtong University and Duke University Institutional Review Boards. Informed consent, physical examination data, and hand X-ray images were collected. At the same time, saliva and nail samples were collected for genetic and biochemical analyses. Brachydactyly was identified by the inability of the fingers (of either hand) to flex sufficiently to touch the palm beyond the transverse skin fold of the hand. ROM was quantified as normal, mildly restricted, moderately restricted or severely restricted for 8 joint sites (cervical spine, shoulder, elbow, wrist, hip, knee, tibiotalar and subtalar ankle, and metatarsalphalangeal foot joint). Non-parametric rank sum test were used to evaluate the severity of ROM abnormalities between the two groups. All statistical analyses were performed with JMP 7.0.
Results: A total of 47 (37.6%) subjects met criteria for brachydactyly. The mean age and body mass index were similar for the brachydactyly and non-brachydactyly groups (Figure 1). The joint ROM was significantly different between the brachydactyly and non-brachydactyly groups for all joint sites except the hip (shoulder and metatarsalphalangeal joints $P<0.05$; cervical spine, elbow, wrist, knee and ankle joints $P<0.001$) (Figure 2). There was a trend for more severe ROM abnormalities on the right side.
Conclusions: In a cohort from the Kashin-Beck Disease region of central China, brachydactyly was associated with more severe joint ROM abnormalities of all major joint groups except the hip. These data demonstrate the widespread and severe nature of the KBD osteoarthropathy as well as the utility of the feature of brachydactyly to identify a more severely affected subgroup.

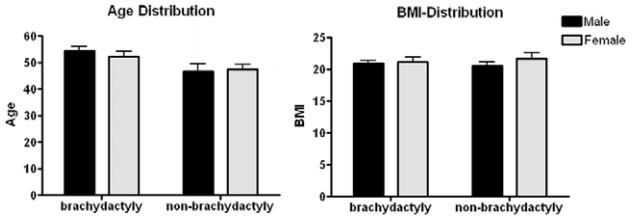

Figure 1

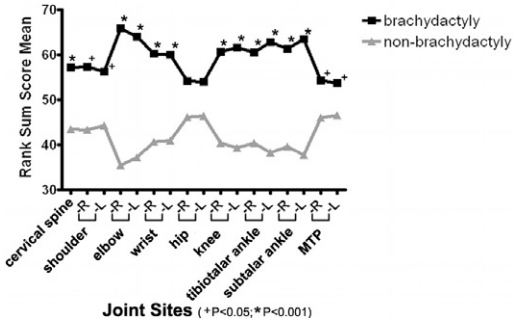

Figure 2. Joint range of motion of 8 joint sites.

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DISEASE MODIFYING DRUGS IN KNEE OSTEOARTHRITIS: CAN THEY BE COST-EFFECTIVE?

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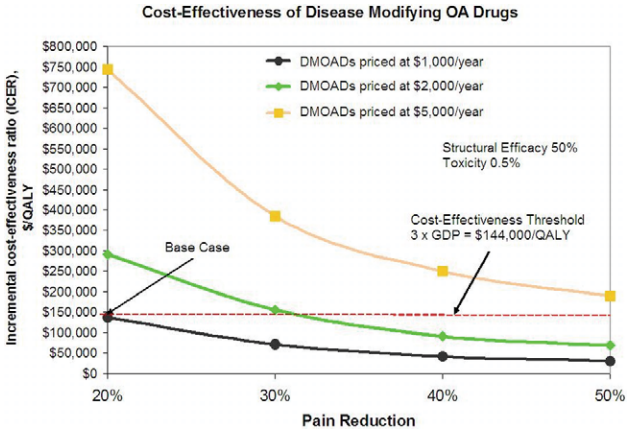
Purpose: One objective of disease modifying drugs in osteoarthritis is to slow cartilage degeneration. Our goal was to determine efficacy and toxicity thresholds under which disease modifying osteoarthritis drugs (DMOADs) would be a cost-effective addition to the current management of knee OA.
Methods: We developed a computer simulation model of the natural history and management of knee OA. We considered a population with a mean age of 62 and symptomatic knee OA equally distributed between K-L 2 and 3. We based the standard of care for knee OA on ACR treatment guidelines, including pain management, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDS), intra-articular steroid injections and total knee arthroplasty (TKA) for those who reached end stage (K-L 4) and were willing to undergo surgery (~30%, based on published literature). We examined DMOAD characteristics along four domains: structural efficacy (inhibiting progression to the next Kellgren Lawrence (K-L) grade), pain efficacy (proportion of those who experience pain relief, independent of structural effect), toxicity, and costs. In the base case analysis we assumed that DMOADs exhibit structural efficacy of 50%, pain efficacy of 20% and severe toxicity of 0.5%/year at annual cost of $1,000. This toxicity level is consistent with the toxicity of biologic therapy for RA. Cost-effectiveness of DMOADs was estimated as the ratio of incremental costs to incremental effectiveness (difference in quality-adjusted life years, QALYs) when DMOADs were added to the current standard of care for knee OA. Both costs and quality adjusted life expectancy were discounted at 3% per year. We used the WHO's recommended threshold for cost-effectiveness (3x per capita GDP=$144,000 in the US). In sensitivity analyses we varied the structural efficacy from 25-75%, pain efficacy from 0-50%, toxicity from 0.1-2% and annual costs from $1,000-$5,000.
Results: In the base case analysis, DMOADs led to a mean improvement of 0.03 QALYs at an additional cost of $3,526, resulting in a cost-effectiveness ratio of $136,000/QALY. Reducing the annual risk of major toxicity to 0.1% led to a cost-effectiveness ratio of $91,000/QALY. Reductions in pain efficacy below 20% or increases in toxicity rates above 0.5%/year led to an overall decrease in QALYs while increasing the cost of OA management in strategies containing DMOADs compared to current standard of care. The cost-effectiveness of DMOADs improved if pain efficacy increased above 20%. (Figure) DMOADs priced at $5,000 per year reached the cost-effectiveness threshold only when they carried no toxicity and were accompanied by both structural and pain efficacy of at least 75%.
Conclusions: Disease modifying regimens focused on slowing progression of symptomatic knee OA may improve quality adjusted life expectancy at cost-effectiveness levels comparable to



other accepted therapies if they also lead to pain relief independent of slowing cartilage degeneration. Toxicity is a key factor affecting their cost-effectiveness. DMOADs priced at greater than $5,000/year are unlikely to be cost-effective by current US standards.

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STAGE OF OSTEOARTHRITIS AND THE LIKELIHOOD OF CARTILAGE THICKNESS LOSS OR GAIN OVER TWO YEARS

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Purpose: The relatively small average annual loss of cartilage in osteoarthritic knees using quantitative MRI techniques may be due to a heterogeneous sampling of knees with cartilage thinning and knees with cartilage thickening (possibly due to swelling or hypertrophy). Cartilage thickening at the early stages of radiographic disease in humans has recently been reported. An understanding of the disease stage at which cartilage thickening and thinning each reach their peak prevalence may inform conceptualization of the natural history of cartilage change in knee OA and enhancement of trial design for disease-modifying interventions. There should be proportionately more knees with cartilage thickness increase at earlier disease stages when swelling and/or anabolic processes may dominate, than at later disease stages. We determined the percentage of knees with cartilage thinning and thickening within specific subregions and tested the hypothesis that knees at moderate to severe stages of osteoarthritic disease were more likely to experience cartilage loss and less likely to experience cartilage thickening over a two year follow-up interval compared to mildly diseased knees.

Methods: All participants had knee OA by definite osteophytes and underwent MRI including double oblique coronal FLASHwe sequences at baseline and two years later. Cartilage thickness was determined in the medial tibia and weightbearing femur as well as in five tibial and three femoral subregions at baseline and two year follow-up using custom software (Chondrometrics GmbH, Ainring, Germany). Average thickness of the given subregion was analyzed, incorporating denuded areas within the subregion as 0. After excluding knees with definite lateral tibiofemoral OA by x-ray, we used logistic regression with generalized estimating equations (GEE, to account for the correlation between knees within persons) to analyze the relationship between baseline medial OA disease severity (using radiographic joint space grade, OARSI Atlas) and the likelihood of cartilage thickness loss or gain (defined as $\geq$ 5%) between baseline and two years later.

Results: We studied 244 knees from 150 persons [mean age 66 years ($\pm$ 11, S.D.), mean BMI 30 ($\pm$ 6), 74% women]. At most surfaces and subregions, the percentage of knees with cartilage thickness decrease (Table 1) tended to be higher and the percentage of knees with cartilage thickness increase (Table 2) tended to be lower in knees with higher (worse) medial joint space grades at baseline than knees with less severe medial disease at baseline. Baseline medial joint space grade 2-3 (vs. 0-1 reference)

Abstract 356 – Table 1. Relationship Between Baseline Medial Joint Space Grade and CARTILAGE THICKNESS LOSS

Surface or subregion of cartilage thickness quantification (all medial)	In knees (n=195) with baseline medial joint space grade = 0-1, # (%) with baseline-to-two year thickness LOSS	In knees (34) with baseline medial joint space grade = 2, # (%) with thickness LOSS	In knees (15) with baseline medial joint space grade = 3, # (%) with thickness LOSS	OR (95% CI) for thickness LOSS associated with baseline medial joint space grade 2-3 (vs. 0-1 reference)
Tibia	32 (16%)	17 (50%)	10 (67%)	6.25 (3.17, 12.33)
Weightbearing (WB) femur	54 (28%)	15 (44%)	8 (53%)	2.31 (1.15, 4.64)
Tibia, central subregion	49 (25%)	21 (62%)	12 (80%)	6.15 (2.84, 13.28)
Tibia, external subregion	56 (29%)	25 (74%)	12 (80%)	7.65 (3.45, 17.00)
Tibia, internal subregion	35 (18%)	11 (32%)	4 (27%)	2.02 (0.99, 4.09)
Tibia, anterior subregion	60 (31%)	16 (47%)	11 (73%)	2.76 (1.46, 5.22)
Tibia, posterior subregion	42 (22%)	15 (44%)	9 (60%)	3.50 (1.77, 6.93)
WB femur, central subregion	64 (33%)	17 (50%)	9 (60%)	2.31 (1.22, 4.39)
WB femur, external subregion	53 (27%)	18 (53%)	10 (67%)	3.57 (1.76, 7.24)
WB femur, internal subregion	56 (29%)	10 (29%)	7 (47%)	1.32 (0.70, 2.48)

Abstract 356 – Table 2. Relationship Between Baseline Medial Joint Space Grade and CARTILAGE THICKNESS GAIN

Surface or subregion of cartilage thickness quantification (all medial)	In knees (n=195) with baseline medial joint space grade = 0-1, # (%) with baseline-to-two year thickness GAIN	In knees (34) with baseline medial joint space grade = 2, # (%) with thickness GAIN	In knees (15) with baseline medial joint space grade = 3, # (%) with thickness GAIN	OR (95% CI) for thickness GAIN associated with baseline medial joint space grade 2-3 (vs. 0-1 reference)
Tibia	17 (9%)	1 (3%)	0 (0%)	0.22 (0.03, 1.62)
Weightbearing (WB) femur	26 (13%)	3 (9%)	1 (7%)	0.58 (0.19, 1.74)
Tibia, central subregion	29 (15%)	3 (9%)	0 (0%)	0.37 (0.11, 1.25)
Tibia, external subregion	28 (14%)	3 (9%)	2 (13%)	0.68 (0.26, 1.75)
Tibia, internal subregion	25 (13%)	2 (6%)	2 (13%)	0.60 (0.20, 1.85)
Tibia, anterior subregion	41 (21%)	6 (18%)	1 (7%)	0.63 (0.22, 1.81)
Tibia, posterior subregion	29 (15%)	7 (21%)	0 (0%)	0.95 (0.36, 2.51)
WB femur, central subregion	36 (18%)	4 (12%)	4 (27%)	0.86 (0.34, 2.16)
WB femur, external subregion	42 (22%)	5 (15%)	2 (13%)	0.61 (0.24, 1.55)
WB femur, internal subregion	23 (12%)	3 (9%)	3 (20%)	1.04 (0.41, 2.65)